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Abstract: Objective: Trauma is a potent exposure that can have implications for health. However, little research has considered whether trauma exposure is related to endothelial function, a key process in the pathophysiology of cardiovascular disease (CVD). We tested whether exposure to traumatic experiences was related to poorer endothelial function among midlife women, independent of CVD risk factors, demographic factors, psychosocial factors, or a history of childhood abuse. Methods: In all, 272 nonsmoking perimenopausal and postmenopausal women aged 40 to 60 years without clinical CVD completed the Brief Trauma Questionnaire, the Child Trauma Questionnaire, physical measures, a blood draw, and a brachial ultrasound for assessment of brachial artery flow-mediated dilation (FMD). Relations between trauma and FMD were tested in linear regression models controlling for baseline vessel diameter, demographics, depression/anxiety, CVD risk factors, health behaviors, and, additionally, a history of childhood abuse. Results: Over 60% of the sample had at least one traumatic exposure, and 18% had three or more exposures. A greater number of traumatic exposures was associated with lower FMD, indicating poorer endothelial function in multivariable models (beta, [standard error, SE] −1.05 [0.40], P = 0.01). Relations between trauma exposure and FMD were particularly pronounced for three or more trauma exposures (b [SE] −1.90 [0.71], P = 0.008, relative to no exposures, multivariable). Conclusions: A greater number of traumatic exposures were associated with poorer endothelial function. Relations were not explained by demographics, CVD risk factors, mood/anxiety, or a by history of childhood abuse. Women with greater exposure to trauma over life maybe at elevated CVD risk.

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Trauma exposure and endothelial function among midlife women

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Abstract

Objective: Trauma is a potent exposure that can have implications for health. However, little research has considered whether trauma exposure is related to endothelial function, a key process in the pathophysiology of cardiovascular disease (CVD). We tested whether exposure to traumatic experiences was related to poorer endothelial function among midlife women, independent of CVD risk factors, demographic factors, psychosocial factors, or a history of childhood abuse.

Methods: In all, 272 nonsmoking perimenopausal and postmenopausal women aged 40 to 60 years without clinical CVD completed the Brief Trauma Questionnaire, the Child Trauma Questionnaire, physical measures, a blood draw, and a brachial ultrasound for assessment of brachial artery flow-mediated dilation (FMD). Relations between trauma and FMD were tested in linear regression models controlling for baseline vessel diameter, demographics, depression/anxiety, CVD risk factors, health behaviors, and, additionally, a history of childhood abuse.

Results: Over 60% of the sample had at least one traumatic exposure, and 18% had three or more exposures. A greater number of traumatic exposures was associated with lower FMD, indicating poorer endothelial function in multivariable models (beta, β [standard error, SE] −1.05 [0.40], $P = 0.01$). Relations between trauma exposure and FMD were particularly pronounced for three or more trauma exposures (b [SE] −1.90 [0.71], $P = 0.008$, relative to no exposures, multivariable).

Conclusions: A greater number of traumatic exposures were associated with poorer endothelial function. Relations were not explained by demographics, CVD risk factors, mood/anxiety, or a by history of childhood abuse. Women with greater exposure to trauma over life maybe at elevated CVD risk.

Key Words: Cardiovascular diseases – Endothelial dysfunction – Flow-mediated Dilation – Trauma – Women.

Cardiovascular diseases (CVDs) are the leading cause of death in women.[1] Psychosocial factors are increasingly appreciated to be important to the development of CVD.[2,3] One potent psychosocial exposure is trauma. Exposure to trauma is particularly prevalent among women. For example, the National Institute of Justice's National Violence Against Women Survey indicated a lifetime incidence of assault of 51.1% among US women,[4] and the Centers for Disease Control and Prevention report that 43.9% of women will experience sexual violence during their lifetime.[5]

While trauma is a well-established risk factor for mental health problems, emerging data indicate its potential importance to the development of chronic disease. Some data indicate that a history of trauma exposure may be associated with increased risk for CVD.[6-11] However, there are several limitations to this work. Most existing work considers self-reported CVD outcomes, findings which are limited by potential biases in CVD event detection and reporting.[12,13] Use of subclinical CVD measures among women who do not yet have clinical CVD can address this limitation. In fact, use of subclinical CVD indices is important when studying midlife women, among whom rates of clinical CVD are low.[14,15] One measure of the vasculature indexes the vascular endothelium, the single cell layer lining the vessel critical to multiple aspects of vascular health and function. Endothelial injury and dysfunction is an initiating event in atherosclerosis,[16] and measures of endothelial function are prospectively associated with later CVD.[17] Finally, as opposed to inquiring

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about trauma among individuals with CVD, investigation of the trauma-CVD risk association in individuals who have not yet experienced a CVD event is important, as the CVD event itself can represent a traumatic exposure.[6,18,19]

Among nonsmoking midlife women free of clinical CVD, we tested whether women with more traumatic exposures over life would have poorer endothelial function at midlife. We hypothesized that associations between trauma exposure and endothelial dysfunction would persist controlling for critical factors, including standard and novel CVD risk factors, depressed mood, and anxiety. Given documented relations of a history of childhood abuse with CVD risk[20,21] and relations of a history of childhood abuse with risk for later adult trauma exposure,[22] we also consider the role of a history of childhood abuse in associations between trauma exposure and endothelial function at midlife.

METHODS

Study sample

We recruited 304 late perimenopausal (2-12 months amenorrhea) and postmenopausal ($\geq$12 months amenorrhea)[23] nonsmoking women aged 40 to 60 years from the surrounding community (Pittsburgh, PA). As women were recruited into a study on hot flashes, by design, half of the women reported daily hot flashes, and half reported no hot flashes in the past 3 months (for further details on study design and sample characteristics, see[24]). Exclusion criteria included hysterectomy and/or bilateral oophorectomy; history of heart disease, stroke, arrhythmia, gynecological cancer, pheochromocytoma, pancreatic tumor, kidney failure, seizures, Parkinson's disease, Raynaud's phenomenon; current pregnancy; or having used the following medications in the past 3 months: oral/transdermal estrogen or progesterone, selective estrogen receptor modulators, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, gabapentin, insulin, beta blockers, calcium channel blockers, alpha-2 adrenergic agonists, or other antiarrhythmic agents. Women who were undergoing chemotherapy, hemodialysis, or peritoneal dialysis were also excluded.

Of the 304 women, 32 women were excluded due to missing flow-mediated dilation (FMD) data because of poor scan quality or movement during the examination. Excluded women did not differ on any study variables than included women. In all, 272 women were included in primary models.

Design and procedures

Women were recruited from the community via advertisements, mailings, and online message boards. Participants underwent physical measurements, ambulatory monitoring, a blood draw, and a carotid artery ultrasound. Procedures were approved by the University of Pittsburgh Institutional Review Board. Participants provided written, informed consent.

Measures

Trauma and abuse exposure

Trauma exposure in adulthood was assessed via items from the Brief Trauma Questionnaire developed for the Nurses' Health Study II (NHS II),[25] which was adapted from the Brief Trauma Interview.[26,27] This brief self-report questionnaire is designed to assess a history of traumatic events, and the version administered in the present study included nine items querying about the following specific events rated as yes or no having ever occurred: serious accidents, natural disasters, life-threatening illness, being beaten or mugged, unwanted sexual contact, death of a child, sexual harassment, threat of injury or violence, or witnessing a severe injury or death. As reported by Koenen et al,[25] inter-rater reliability for the presence of criterion A1 trauma exposure according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) was high (average kappa = 0.70 [range 0.74-1.00] for all events, except illness [0.60]). Exposures were considered separately, and also summed, with the sum categorized as none, 1 to 2, or 3 or more exposures.

Child abuse history was assessed via a separate questionnaire, the 28-item Child Trauma Questionnaire (CTQ), a validated measure of child abuse and neglect experienced at or before age 18.[28] It included questions about emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect. The CTQ has strong test-retest reliability (0.79-0.86), internal consistency ($\alpha = 0.75-0.94$), and convergent validity.[28,29] The CTQ was considered as a total continuous scale score.

Brachial ultrasound

After an overnight fast, FMD was measured after 10 minutes of supine rest by high-resolution B-mode ultrasound imaging of the right brachial artery, 2 to 10 cm proximal to the antecubital crease, by trained sonographers using a standardized protocol. Images were obtained at rest (baseline) and after 5 minutes of forearm blood flow occlusion (postdeflation) with a pneumatic tourniquet set to 50 mm Hg above the participant's systolic blood pressure (SBP). For baseline diameters, digitized images were recorded for 20 seconds. Immediately after deflation, images were recorded continuously for 3 minutes. The arterial diameter was measured as the distance between the anterior and posterior arterial wall media-adventitia interfaces on images captured on the R wave using edge-detection software. All images for this study were read by a single trained reader using the Brachial Analysis System (MIA, University of Iowa) software.[30] The reading software allows continuous tracking of the brachial artery diameter across these images so that the peak change in diameter can be accurately determined. FMD was calculated as the maximum percentage of change in arterial diameter, relative to baseline. This methodology at this laboratory has shown reproducibility (intraclass correlation coefficient = 0.70-0.72).[31]

Covariates

Height and weight were measured via a fixed stadiometer and a calibrated balance beam scale, and body mass index (BMI) calculated (kg/m^2). Seated blood pressure (BP) was measured via a Dinamap device after 10-minute rest. Women reported a lifetime history of a range of psychiatric disorders, including post traumatic stress disorder (PTSD). Medical and

reproductive history was assessed by standard instruments. Menopausal status was obtained from reported menstrual bleeding patterns.[23] Parity was classified by the total reported number of live births. Use of medications (antidepressants, antihypertensives, lipid-lowering, glucose-lowering, beta agonists, anticonvulsants) was reported. Anxiety was assessed via the State-Trait Anxiety Inventory,[32] depressive symptoms by the Center for Epidemiologic Studies Depression scale,[33] perceived stress via the Cohen perceived stress scale,[34] and sleep quality via the Pittsburgh Sleep Quality Index.[35] Leisure-time physical activity was assessed via the International Physical Activity Questionnaire.[36] Hot flashes were assessed by 24-hour ambulatory physiologic monitoring.[24] Sleep time was assessed over 3 days via actigraphy (Actiwatch 2, Respironics, Inc., Murrysville, PA) in 1-minute epochs, and analyzed and scored (Philips Actiware v6.0.0 software) according to established methods.[37] Total sleep time was calculated as: ([time in bed] − [sleep onset latency] − [minutes of wakefulness between sleep onset time and final wake time]). Glucose, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured enzymatically (Vital Diagnostics, Lincoln, RI; intra-assay and inter-assay coefficients of variation [CVs], respectively, were: glucose—1.9%, 2.4%; HDL—1.8%, 2.6%; triglycerides—1.8%, 3.7%). Total cholesterol was determined enzymatically (intra-assay and inter-assay CVs: 3.5% and 6.7%) and low-density lipoprotein (LDL-C) was calculated using the Friedewald formula.[38] Insulin was measured via radioimmunoassay (intra-assay and inter-assay CVs: 4.8% and 10.5%). Homeostatic model assessment (HOMA), reflecting insulin resistance, was calculated.[39] C-reactive protein (CRP) was assessed using a high sensitivity reagent set (Beckman Coulter, Brea, CA; intra-assay and inter-assay CVs: 5.5% and 3.0%). Interleukin (IL)-6 was assessed with an R&D Systems high sensitivity ELISA (Minneapolis, MN; intra-assay and inter-assay CVs: 9.1% and 10.2%).

Data analysis

Sum of trauma exposures, HOMA, triglycerides, CRP, and IL-6 values were natural log-transformed and leisure time physical activity square root-transformed for analysis. Differences between participants by included/excluded status were tested using linear regression, Wilcoxon rank-sum, and chi-square tests. Associations between trauma exposure and FMD were tested in linear regression models. Covariates were factors associated with FMD at $P < 0.20$: baseline lumen diameter, age, race/ethnicity, leisure time physical activity, state anxiety, parity, beta agonist medications. BMI and SBP were forced into models. To test the role of childhood abuse in relations between lifetime trauma exposure and FMD, a separate set of models included CTQ scores as an additional covariate in multivariable models testing relations between Brief Trauma Questionnaire scores in relation to FMD. We also tested interactions between CTQ scores and Brief Trauma Questionnaire scores in relation to FMD in multivariable models. In secondary models, a reported history of PTSD (six women) was considered as an additional covariate or as an exclusion. Additional covariates were education, financial strain, depressive symptoms, perceived stress, antidepressants, general self-rated health, lipids, HOMA, BP-lowering, lipid-lowering, and diabetes medications, hot flashes, CRP, and IL-6. Residual analysis and diagnostic plots were conducted to verify model assumptions. Analyses were performed with SAS v9.2 (SAS Institute, Cary, NC). Models were two-sided at $\alpha = 0.05$.

RESULTS

Participants were on average 54 years old, postmenopausal, overweight, and white (Table 1). The mean (SD) FMD was 7.39% (4.04). Over 60% (n = 164) of the sample had at least one traumatic exposure. Eighteen percent of the women had three or more traumatic exposures (Table 2). The most common exposure was unwanted sexual contact, reported by 22% of the women.

Women with a greater number of traumatic exposures, particularly three or more, had lower FMD—an indicator of poorer endothelial function (Table 3; Fig. 1). The single exposure most strongly associated with lower FMD was having a history of a major accident. Associations were not explained by covariates associated with FMD. We also considered a range of additional covariates, including educational attainment, additional CVD risk factors, and additional cardiovascular medications, and relations persisted.

We considered the role of childhood abuse in these relations. As expected, the correlation between a history of trauma exposure (Brief Trauma Questionnaire score) and childhood abuse (CTQ score) was moderate and statistically significant ($\rho = 0.26$, $P < 0.0001$). When including childhood abuse history in multivariable models of lifetime trauma exposure in relation to FMD, associations between lifetime trauma and FMD persisted (Table 3). There was no evidence of a synergy between child abuse and lifetime trauma exposure, as interactions between trauma exposure and childhood abuse in relation to FMD were not significant ($P > 0.20$).

We conducted several additional analyses. We considered additional covariates of depressive symptoms, perceived stress, hot flashes, self-rated health, financial strain, alcohol use, sleep, and inflammatory markers (CRP, IL-6), and findings were unchanged (data not shown). Six women reported a history of PTSD. To consider whether findings were driven by these women with PTSD, we first included PTSD as an additional covariate, and next alternatively excluded women with PTSD, and findings remained (data not shown). We considered any differences in relations between trauma exposure and FMD by race/ethnicity; interactions were not significant (interaction $P > 0.10$). Given prior evidence of modification of relations of trauma exposure and cardiovascular outcomes by sleep time,[40] we additionally explored whether sleep time modified associations between trauma exposure and FMD. We found indication of interaction between accident history and actigraphy-assessed sleep time (interaction $P = 0.03$), with relations between accident history

TABLE 1. *Sample characteristics*

	Trauma exposure	
	Yes (n = 164)	No (n = 108)
Age, M (SD)	54.13 (3.94)	54.00 (3.93)
Race, n (%)		
White	119 (72.56)	79 (73.15)
African American, Hispanic, other	45 (27.44)	29 (26.85)
BMI, M (SD)	28.57 (6.30)	29.74 (7.52)
SBP, mm Hg, M (SD)	120.6 (15.25)	117.8 (12.83)
DBP, mm Hg, M (SD)	70.31 (9.32)	69.38 (8.62)
HDL, M (SD)	62.64 (15.54)	62.86 (13.48)
LDL, M (SD)	131.5 (34.27)	130.4 (33.19)
Triglycerides, M (SD)	113.52 (66.62)	103.21 (44.13)
HOMA, M (SD)	2.67 (1.61)	2.68 (1.70)
Parity, Median (IQR)	2.0 (1, 3)	2.0 (1, 3)
Self-rated health, n (%)		
Excellent	40 (24.39)	31 (38.70)
Very good	70 (42.68)	52 (48.15)
Good/fair/poor	54 (32.93)	25 (23.15)
Education, n (%)		
High school, vocational school	63 (38.41)	51 (47.22)
College education or higher	101 (61.59)	57 (52.78)
Financial strain (yes), n (%)	51 (31.10)	32 (29.63)
Physical activity, leisure time, IPAQ, M (SD)	786.76 (1113.16)	982.03 (1135.28)
State anxiety (Speilberger), M (SD)	32.18 (10.04)	32.24 (9.66)
Depressive symptoms (CESD), M (SD)	8.24 (8.37)	7.26 (7.89)
Perceived stress, M (SD)	4.59 (2.95)	4.42 (2.80)
Childhood abuse/neglect (CTQ score), M (SD)	39.86 (14.78)	32.76 (9.92)
Hot flashes, physiologic, number/24 h, M (SD)	9 (9)	8 (8)
CRP, M (SD)	2.89 (3.48)	3.05 (3.86)
IL-6, M (SD)	1.99 (1.83)	2.04 (2.82)
Medications, n (%)		
BP-lowering	23 (14.02)	22 (20.37)
Lipid-lowering[a]	15 (9.15)	21 (19.44)
Diabetes	6 (3.66)	4 (3.70)
Beta-agonist	7 (4.27)	7 (9.48)
Anticonvulsants	3 (1.83)	0 (0.00)
Antidepressants	3 (1.83)	3 (2.78)

Depressive symptoms, triglycerides, HOMA, IL-6, CRP log-transformed, physical activity square root-transformed for comparison.
BMI, body mass index; BP, blood pressure; CESD, Center for Epidemiologic Studies Depression Scale; CRP, C-reactive protein; CTQ, Child Trauma Questionnaire; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; IL-6, interleukin 6; IPAQ, International Physical Activity Questionnaire; IQR, interquartile range; LDL, low-density lipoprotein; M, mean; SBP, systolic blood pressure; SD, standard deviation.
[a]Differs between trauma exposure group at $P < 0.05$.

and lower FMD particularly pronounced among women sleeping <6 hours per night (<6 hours: $\beta = -2.87$, SE = 1.17, $P = 0.02$; ≥6 hours: $\beta = -1.36$, SE = 0.72, $P = 0.06$).

DISCUSSION

In this sample of nonsmoking midlife women free of clinical CVD, women with a history of trauma exposure, particularly three or more traumatic exposures, had lower FMD, indicating poorer endothelial function. Associations between trauma exposure and endothelial function were not explained by multiple potentially confounding or explanatory factors, including psychosocial or demographic factors, mood, anxiety, CVD risk factors, or even a history of childhood abuse or neglect. These data support the importance of considering trauma exposure as an important psychosocial factor in midlife women's cardiovascular health.

Prior work has linked trauma exposure to reported cardiovascular outcomes.[9,41] The present finding is novel in its use of vascular ultrasound measures of endothelial function among individuals free of CVD. Use of vascular ultrasound provides a subclinical disease marker and can indicate potential early vascular dysfunction before clinical disease is present. Considering subclinical indicators is useful for indexing aspects of cardiovascular health among midlife women, who typically show clinical CVD only decades later.[1,14] Further, using subclinical measures among an asymptomatic population avoids potential biases associated with self-reported CVD (eg, contact with the medical system, health literacy),[12,13] and provides the opportunity for intervention and prevention before frank disease is present. Finally, investigating subclinical CVD before clinical CVD is evident avoids the potentially interpretative difficulty of the clinical CVD event itself (eg, heart attack, stroke) serving as a trauma.[19] In sum, the present data underscore the importance of particular prevention efforts aimed at women with a history of multiple traumatic exposures, and this work may also point to a possible mechanism, endothelial dysfunction, linking trauma exposure to later clinical CVD.

Over 60% of the women in this study reported exposure to one or more traumatic experiences, and 18% of the women endorsed three or more traumatic exposures. These figures are consistent with other work.[9] Women with a greater number of exposures had the lowest FMD, pointing to the importance of multiple lifetime exposures.[41] The most common exposure was a history of sexual assault, reported by 22% of the women, yet the exposure most strongly related to endothelial function was having been in an accident (18% of the sample). We considered an explanatory factor of ongoing physical health issues in these relations, yet associations persisted with adjustment for a range of physical health measures, including

TABLE 2. *Prevalence of exposure to traumatic events*

	N (%)
Have you ever...	
Been in a serious car accident or a serious accident?	49 (18.01)
Been in a major natural or human made disaster?	26 (9.56)
Had a very serious or life-threatening illness?	17 (6.25)
Been attacked, beaten or mugged by anyone?	53 (19.49)
Been made or pressured into having some type of unwanted sexual contact?	60 (22.06)
Experienced the death of one of your own children?	18 (6.62)
Experienced sexual harassment at work that was either physical or verbal?	53 (19.49)
Been in any other situation in which you were seriously injured?	37 (13.6)
Witnessed a situation in which someone was seriously injured or killed?	58 (21.32)
Sum exposures	
0	108 (39.71)
1-2	114 (41.91)
3+	50 (18.38)

TABLE 3. *Relation between trauma exposure and FMD*

	FMD (%) B (SE)		
	Model 1	Model 2	Model 3
Serious accident	−1.65 (0.59)[a]	−1.61 (0.62)[b]	−1.78 (0.60)[a]
Disaster	−1.27 (0.78)	−1.25 (0.81)	−1.17 (0.79)
Serious illness	0.41 (0.95)	0.31 (0.98)	0.36 (0.95)
Attacked	−0.58 (0.57)	−0.75 (0.60)	−0.74 (0.60)
Sexual assault	−0.48 (0.55)	−0.44 (0.57)	−0.69 (0.59)
Death of child	−1.22 (0.91)	−1.23 (0.94)	−1.58 (0.95)[c]
Sexual harassment	−0.66 (0.57)	−0.76 (0.60)	−0.95 (0.60)
Serious injury	0.41 (0.66)	0.42 (0.68)	0.22 (0.70)
Witness violence	−0.24 (0.55)	−0.27 (0.57)	−0.48 (0.58)
Any exposure	−0.84 (0.47)[c]	−0.88 (0.49)[c]	−1.03 (0.49)[b]
Sum exposures[d]	−0.73 (0.37)[b]	−0.75 (0.39)[b]	−1.05 (0.40)[a]
Number of exposures[e]			
1-2	−0.64 (0.51)	−0.67 (0.53)	−0.75 (0.51)
3+	−1.30 (0.64)[b]	−1.37 (0.68)[b]	−1.90 (0.71)[a]

Each exposure considered in separate model.
Model 1: Baseline diameter, age, race, BMI, SBP, beta agonist medications, anticonvulsant medications, parity, leisure time physical activity, state anxiety.
Model 2: Model 1 covariates + education, diabetes, HOMA, lipids (LDL, HDL, triglycerides), additional medications (antihypertensive, lipid-lowering, antidiabetic, antidepressant).
Model 3: Model 1 covariates + child trauma history (child trauma questionnaire).
BMI, body mass index; FMD, flow-mediated dilation; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; LDL, low-density lipoprotein; SBP, systolic blood pressure; SE, standard error.
[a]$P < 0.01$.
[b]$P < 0.05$.
[c]$P < 0.10$.
[d]Log-transformed for analysis.
[e]Relative to no exposures.

self-rated health, health status, and markers of inflammation. It is notable that women with a history of major illness in the present study did not have lower FMD than their counterparts without such a history. In sum, the present work indicates that a greater number of traumatic exposures was related to lower FMD.

A notable aspect of the current work was our consideration of both lifetime trauma exposure and child abuse/neglect. Our prior work has found a history of child abuse and neglect associated with greater adult carotid atherosclerosis.[20] However, controlling for childhood trauma exposure, assessed via a validated child trauma inventory, did not reduce associations between trauma and FMD. Further, we found no evidence of an interactive or additive effect of childhood and lifetime trauma in relation to FMD. Findings support an independent association between adult exposures from childhood exposures in relation to CVD risk.

We considered a range of possible confounders and pathways that might account for associations between trauma exposure and endothelial function. Controlling for multiple traditional and novel CVD risk factors, comorbidities, and medications did not explain associations. Controlling for depression, anxiety, and other negative affective symptoms did not reduce associations between trauma exposure and endothelial function, suggesting that the trauma exposure itself was important irrespective of an ongoing affective response to it. Excluding women endorsing a history of PTSD did not alter findings, supporting findings consistent with other work indicating relations between trauma exposures to health outcomes independent of PTSD.[9,41] Finally, neither hot flashes or sleep characteristics explained associations between trauma exposure and FMD. However, there was some evidence that relations between accident history and lower FMD was particularly prominent among women with shorter sleep—a finding broadly consistent with our prior work.[40] Although many pathways were considered here, pathways deserving further investigation in future work include the hypothalamic pituitary adrenal axis,[42] the nitric oxide pathway,[43] and epigenetic alterations,[44,45] mechanisms potentially impacted by traumatic experiences and associated with CVD risk.

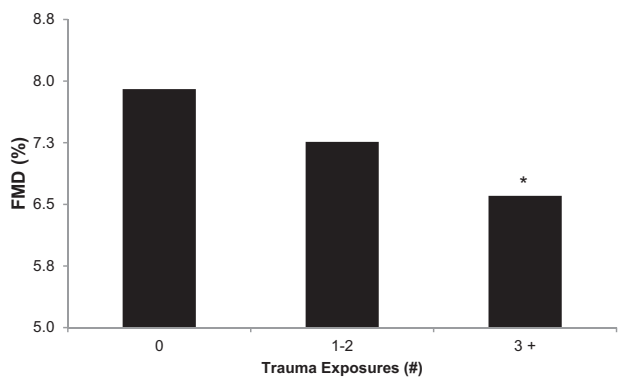

FIG. 1. Adjusted mean FMD by number of traumatic exposures. Means adjusted for baseline diameter, age, race, BMI, SBP, beta agonist medications, anticonvulsant medications, parity, leisure time physical activity, state anxiety. *$P < 0.05$ relative to no exposure. BMI, body mass index; FMD, flow-mediated dilation; SBP, systolic blood pressure.

Several limitations deserve mention. We assessed a range of potential exposures using an adapted measure implemented in other major cohort studies (Nurses' Health Study II). However, not all possible exposures were assessed, and an abbreviated version of this measure was administered (eg, excluding items pertaining to nursing practice). Thus, some misclassification of exposure is possible. Further, women were recalling these exposures rather than assessing them prospectively; thereby these reports may be subject to potential for influences of memory. Further, women reported a history of PTSD, but not all PTSD symptoms were assessed, and PTSD history was not established via diagnostic interview. Although a wide range of possible confounders were assessed and considered carefully, residual confounding is a consideration in observational studies, and this study cannot establish directionality or causality. Further, brachial ultrasound is a validated measure of endothelial function highly correlated with coronary endothelial function[46]; it is not a direct measure, which would require more invasive procedures not amenable to a sample of this size. Finally, the sample included women and had somewhat limited racial ethnic diversity; men and more racially/ethnically diverse samples should be considered in future work.

This study had several strengths. This study included a well-characterized sample of nonsmoking midlife women free of clinical CVD. Vascular endothelial function was assessed via a widely used and validated marker of vascular endothelial function. Multiple possible confounders and mechanisms were measured and considered here. Exposures during both adulthood and childhood were assessed and considered.

CONCLUSIONS

In summary, women with a history of three or more lifetime traumatic exposures had poorer endothelial function than women without a trauma history. The most prevalent exposure was sexual assault, yet the most potent single exposure for endothelial function was a history of having been in an accident. Relations were not explained by psychological factors such as anxiety or depressive symptoms, standard CVD risk factors, general health status, or a childhood history of abuse or neglect. These data underscore the potential value of considering trauma exposure as an important cardiovascular health issue among women.

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